57. The method of claim 36, wherein the superantigen is staphylococcal enterotoxin E.

C4

REMARKS

This is an amendment and response to the Office Action mailed August 16, 1999 in the above-referenced case. It is timely by being filed on or before November 16, 1999. Please note that a change of mailing address for this case is enclosed herewith. Also, a Petition To The Commissioner Under 37 C.F.R. § 1.181 From Improper Requirement For Restriction is being submitted with this paper.

Claims 14-35 have been provisionally canceled pending the outcome of the instantly co-filed Petition To The Commissioner Under 37 C.F.R. § 1.181 From Improper Requirement For Restriction. Claims 39-43 and 48-51 have been canceled without prejudice. New claims 52-57 have been added. The Specification has been amended. Claims 36-38, 44-47, and 52-57 are active and pending (and possibly claims 14-35 depending on the outcome of the Petition To The Commissioner).

In the Office Action, claims 36-51 were rejected under 35 U.S.C. § 112, first paragraph; claims 42 and 51 were rejected under 35 U.S.C. § 112, second paragraph; claims 36-51 were rejected under 35 U.S.C. § 103 over Dohlsten et al.; and changes to the formal drawings, abstract and brief description of the drawings were requested.

For the reasons set forth herein including the amendments, applicants respectfully submit that the presently amended claims are in condition for allowance. A Notice Of Allowance is therefore respectfully requested.

The amended claimed subject matter is patentable under Section 112, first paragraph, as agreed by the Examiner

In the Office Action the Examiner agreed that the "specification [discloses] the use of specific staphylococcal enterotoxins in the claimed invention as per claim 7." Solely in applicants' business interest of advancing rapid allowance of claims in this case (especially considering that the first substantive Office Action on the merits in this case was not issued until more than two years from the filing date), reserving all rights to canceled subject matter, and not in acquiescence, applicants have amended the presently claimed subject matter to track that which the Examiner has indicated is allowable under Section 112, first paragraph. Claim 36 has been amended to the superantigens of claim 7 which the Examiner indicated are supported by the specification. All claims are therefore allowable under 35 U.S.C. Section 112, first paragraph.

The claims are allowable under Section 112, second paragraph

The Examiner rejected claims 42 and 51 under 35 U.S.C. § 112, second paragraph. These claims have been canceled, thereby obviating the Section 112, second paragraph, rejection.

The claimed subject matter is patentable over Dohlsten et al.

The Examiner rejected the claimed subject matter under Dohlsten et al. 1991 (PNAS USA 88, 9287-9291) based upon the argument that: i) mutations in the instant case that reduce MHC Class

II antigen binding are allegedly in the C-terminal region of superantigens, and ii) Dohlsten allegedly suggests making mutations in the C-terminal region of superantigens in order to reduce Class II MHC antigen binding. Applicants respectfully disagree and assert that the claimed invention is not obvious over any prior art of record because, *inter alia*, Dohlsten does not accurately teach or suggest making mutations in any particular region of any superantigens in order to affect Class II MHC antigen binding, including the C-terminal region, and further still, the claimed and supported invention is not limited to making mutations in the C-terminal region of superantigens in order to affect Class II MHC binding.

In the Office Action, the Examiner acknowledges that Dohlsten does not teach that the superantigen portion of the conjugate has been mutated to show a modified ability to bind Class II MHC antigen.

However, the Examiner interprets statements in Dohlsten to teach that the Class II binding site in superantigens is in the C-terminal region, and that mutations in the C-terminal region of superantigens could reduce Class II MHC binding. However, in fact, Dohlsten does not clearly teach that the Class II MHC antigen binding site in superantigens is in the C-terminal region (and therefore does not suggest that mutations in the C-terminal region of superantigens could reduce Class II MHC binding).

The statements in the Dohlsten paper that allegedly teach that Class II MHC binding is in the C-terminal region of superantigens are: i) a reference to unpublished work that a "recombinant C-terminal fragment of SEA contains MHC Class II binding determinants," (page 9291, left column, "G.H. unpublished") and ii) "studies on SEC1 and toxic shock syndrome toxin 1 support a C-terminal location for the MHC Class II binding epitopes." (page 9291, left column, "refs. 33, 34")

These statements, taken alone or in combination, do not in fact teach that Class II MHC binding is in the C-terminal region of superantigens. Regarding the first point, subsequent publication of the paper referred to as "G.H. unpublished" revealed that the work referred to was with a fragment of SEA comprising more than one half of the entire SEA protein (AA 107-233) wherein MHC Class II binding activity was recognized. This does not focus MHC Class II antigen binding activity to the C-terminal region of superantigens.

Further, the second statement, "studies on SEC1 and toxic shock syndrome toxin 1 support a C-terminal location for the MHC Class II binding epitopes," is, in fact, not correct when referring to the location for MHC Class II binding on SEC1 and toxin shock syndrome toxin 1. An immense body of work has shown that the MHC Class II binding region of SEB (structural homologue of SEC1) and TSST-1 resides in the N-terminal part of the protein and not in the C-terminal (see, e.g., Kim et al., Science, 1994, 266:1870 (co-crystals of MHC Class II antigens and TSST-1); and Jardetzky et al., Nature, 1994, 368:711 (SEB and MHC Class II binding)).

Hence, Dohlsten et al. does not clearly teach or suggest that the C-terminal region of superantigens is responsible for MHC Class II antigen binding. Hence, the reference does not teach or suggest making mutations in the C-terminal region of superantigens in order to reduce Class II MHC antigen binding.

The present specification (and claimed invention) recognizes and teaches that different regions of superantigens are responsible for binding the MHC Class II antigens and that mutations in these regions can affect MHC Class II binding. For example, on page 23, lines 12-15 it is stated that, regarding the data and teaching on SEA, "our data indicates an involvement of the four residues N128, H187, H225 and D227."

Applicants therefore assert that Dohlsten does not render the presently claimed subject matter obvious. Removal of this rejection is therefore respectfully requested.

Formalities are being complied with

The present submission amends the specification in order to add an Abstract and correctly label the Brief Description of the Drawings. Corrected Formal Drawings are presently being prepared and will be filed.

As supported by the attached Petition, Applicants respectfully disagree with the Examiner's grounds for issuing a Restriction Requirement: The independent claims as initially presented are patentable over the prior art including Buelow

The Examiner is basing the Restriction Requirement upon the position that the independent claims are allegedly not patentable over Buelow, et al., J. Immunol., 1992, 148:1-6. The is incorrect because the Examiner's position is based upon an incorrect interpretation of Buelow.

The Examiner is basing the unpatentability rejection on the following assertion (emphasis added):

> Buelow et al. teach a protein A-SEB conjugate wherein the SEB of the conjugate only contains amino acids 1-130 of SEB (see Figure 4)...[t]his conjugate can bind the VB of a TCR (because it stimulates T cells, see Figure 4)...It is an inherent property

of said mutated conjugate that it has a modified ability to bind MHC class II antigens because it lacks SEB residues important for class II binding (e.g., such as residue 227, see specification, pages 22-23).

This statement is incorrect. The SEB conjugate of Buelow that contains amino acids 1-130 of SEB does not stimulate T cells. As shown in Buelow in Figure 4 and, for example, also on page 5, left column, "[t]he pCA-SEB fusion protein with residues 131-239 at the carboxy terminus deleted [i.e., SEB with amino acids 1-130] had neither mitogenic nor tolerogenic activity."(emphasis added).

Furthermore, Buelow does not in any manner teach, disclose or suggest modifying residues in a full length superantigen in order to affect MHC Class II antigen binding. It is entirely unclear from Buelow which regions of a full length superantigen should be mutated in order to expect a mutant protein with altered MHC Class II binding. The disclosure, teaching and suggestion of Buelow all are directed solely to the *use of truncated pCA-SEB fusion proteins to map to the amino-terminal half of the molecule (residues 1-138) a minimally immunologically active domain of SEB capable of inducing proliferation and anergy in cloned human T cells expressing VB3.1* (see first paragraph of page 2, Buelow). Buelow is not aimed at identifying the MHC Class II binding domain and certainly is not aimed at identifying which residues of full length superantigens may be mutated to specifically alter Class II MHC antigen binding. Buelow provides an indication that the region encompassing residues 1-138 of SEB constitutes a functional (i.e., "immunologically active") domain of the molecule; however, the Buelow authors recognize that it remains to be determined which parts of the molecule are involved in the interactions with Class II MHC antigens and TCR

molecules, for example, directly, and/or indirectly (for example by influencing the conformation of the molecule) (see Discussion section on page 6, Buelow).

Indeed, the actual data presented in Buelow makes it clear that it does not teach or predict anything about Class II MHC antigen binding. For example, F45 and E67 are known to be important for Class II MHC binding in SEB and both the Buelow 1-130 and 1-138 SEB fragments have these identical (wild-type) sequences. However, as discussed above and plainly shown in Buelow, these two proteins have dramatically differing activities; the fragment 1-130 has neither mitogenic nor tolerogenic activity, while 1-138 fragment (identical *but for* the additional eight amino acids which are not in the recognized Class II MHC binding region) has activity. Hence, there is no way that one skilled in the art could gain any information from Buelow about which residues in superantigens are important in Class II MHC binding.

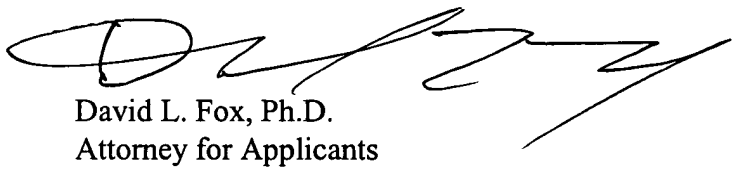
As presented in the attached Petition, Applicants respectfully assert that all claims as originally presented and currently pending (claims 14-38, 44-47 and 52-57) are patentable as a single invention. Withdrawal of the restriction requirement and examination of all claims on the merits is therefore requested.

The Examiner is encouraged to call the undersigned attorney to discuss any matters relating to this case.

Applicants respectfully petition for any extension of time necessary to render this response timely.

Please charge any fees due or credit any overpayment to the standing account of Fulbright & Jaworski L.L.P., Deposit No. 06-2375 under Order No. 984877.

Respectfully submitted,



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